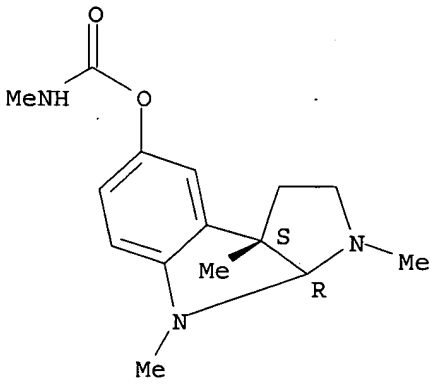
L1 ANSWER 54 OF 54 REGISTRY COPYRIGHT 2003 ACS on STN
RN 57-47-6 REGISTRY
CN Pyrrolo[2,3-b]indol-5-ol, 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, methylcarbamate (ester), (3aS,8aR)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Physostigmine (8CI)**
CN Pyrrolo[2,3-b]indol-5-ol, 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, methylcarbamate (ester), (3aS-cis)-
OTHER NAMES:
CN (-)-Eserine
CN **(-)-Physostigmine**
CN Cogmine
CN Eserine
CN Esromiotin
CN MCV 4484
CN NIH 10421
CN NSC 30782
CN Physostol
FS STEREOSEARCH
DR 511-49-9, 50975-37-6
MF C15 H21 N3 O2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4268 REFERENCES IN FILE CA (1907 TO DATE)
35 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4272 REFERENCES IN FILE CAPLUS (1907 TO DATE)
23 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L3 ANSWER 20 OF 124 USPATFULL on STN

ACCESSION NUMBER: 2003:183843 USPATFULL

TITLE: Compounds and methods for diagnosing and treating amyloid-related conditions

INVENTOR(S): Raub, Thomas J., Kalamazoo, MI, United States
Sawada, Geri A., Portage, MI, United States
Tanis, Steven P., Kalamazoo, MI, United States
Fici, Gregory J., Kalamazoo, MI, United States
Buhl, Allen Edwin, Portage, MI, United States
Carter, Donald Bainbridge, Kalamazoo, MI, United States
Bandiera, Tiziano, Gambolo-Pavia, ITALY
Lansen, Jacqueline, Milan, ITALY
Pellerano, Cesare, Siena, ITALY
Savini, Luisa, Siena, ITALY

PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6589504	B1	20030708	
APPLICATION INFO.:	US 2000-667357		20000922	(9)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-234611P	20000922	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Padmanabhan, Sreeni
ASSISTANT EXAMINER: Willis, Michael A.
LEGAL REPRESENTATIVE: Pharmacia & Upjohn, Darnley, Jr., James D.
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 1195
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides methods for diagnosing and treating amyloid-related conditions and compounds useful for the same. The invention provides for detecting, imaging, monitoring, diagnosing, and treating conditions characterized by the binding or aggregation of amyloid fibrils. More particularly, the invention relates to using quinolinehydrazone compounds for diagnosing and treating amyloidotic conditions and also as an antioxidant.

L3 ANSWER 12 OF 124 USPATFULL on STN

ACCESSION NUMBER:	2003:321515 USPATFULL
TITLE:	Method and composition for modulating amyloidosis
INVENTOR(S):	Reiner, Peter B., Vancouver, CANADA Lam, Fred Chiu-lai, Vancouver, CANADA
PATENT ASSIGNEE(S):	The University of British Columbia, Vancouver, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6660725	B1	20031209
APPLICATION INFO.:	US 2000-643511		20000822 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1998-177413, filed on 23 Oct 1998, now patented, Pat. No. US 6514688
Continuation-in-part of Ser. No. US 1998-67523, filed on 28 Apr 1998, now abandoned Continuation-in-part of Ser. No. US 1997-847616, filed on 28 Apr 1997, now abandoned

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Brumback, Brenda
ASSISTANT EXAMINER:	Gupta, Anish
LEGAL REPRESENTATIVE:	Seed IP Law Group PLLC
NUMBER OF CLAIMS:	3
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	19 Drawing Figure(s); 12 Drawing Page(s)
LINE COUNT:	2468

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for modulating amyloid deposition in a subject are described. An effective amount of at least one ATP binding cassette (ABC) transporter blocker is administered to a subject, such that modulation of amyloid deposition occurs. Methods also include administering and effective amount of at least one ABC transporter blocker, or a pharmaceutically acceptable salt thereof, to a subject such that a disease state associated with amyloidosis is treated. Packaged pharmaceutical compositions for treating amyloidosis are described. The package includes a container for holding an effective amount of a pharmaceutical composition and instructions for using the pharmaceutical composition for treatment of amyloidosis. The pharmaceutical composition includes at least one ABC blocker for modulating amyloid deposition in a subject. Methods for identifying agents which modulate amyloid deposition in a subject are also described. An effective amount of at least one ATP binding cassette (ABC) transporter blocker is administered to an organism, such that modulation of amyloid deposition occurs.

L3 ANSWER 11 OF 124 USPATFULL on STN

ACCESSION NUMBER: 87:30280 USPATFULL

TITLE: Methods for treating leukopenia

INVENTOR(S): Gordon, Arnold Z., 5129 Mayview Rd., Lyndhurst, OH, United States 44124
Rossof, Arthur H., 4334 No. Hazel - 1301, Chicago, IL, United States 60613

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4661509		19870428
APPLICATION INFO.:	US 1984-582068		19840221 (6)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1982-425460, filed on 28 Sep 1982, now abandoned which is a division of Ser. No. US 1981-291062, filed on 7 Aug 1981, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Rosen, Sam

LEGAL REPRESENTATIVE: Niblack & Niblack

NUMBER OF CLAIMS: 8

EXEMPLARY CLAIM: 1,5,6,7,8

LINE COUNT: 282

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of improving the levels of formed blood elements in a patient having disease or therapy induced leukopenia comprising administering to said patient a therapeutically effective amount of a pharmaceutically acceptable, water or lipid soluble tertiary or quaternary amine having cholinergic or anticholinesterase activity.

L3 ANSWER 10 OF 124 USPATFULL on STN

ACCESSION NUMBER:	88:80654 USPATFULL
TITLE:	Memory enhancing and analgesic 1,2,3,3A,8,8A-hexahydro-3A,8 (and) 1,3A,8)-di(and tri)methylpyrrolo(2,3-B)indoles, compositions and use
INVENTOR(S):	Hamer, R. Richard L., Far Hills, NJ, United States Helsley, Grover C., Pluckemin, NJ, United States Glamkowski, Edward J., Warren, NJ, United States Chiang, Yulin, Convent Station, NJ, United States
PATENT ASSIGNEE(S):	Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4791107		19881213
APPLICATION INFO.:	US 1987-49894		19870515 (7)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1986-885991, filed on 16 Jul 1986		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Ramsuer, Robert W.		
LEGAL REPRESENTATIVE:	Ikeda, Tatsuya		
NUMBER OF CLAIMS:	26		
EXEMPLARY CLAIM:	1,20		
LINE COUNT:	1713		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are described compounds of the formula ##STR1## where (a) X is O or S;

(b) R is H, loweralkyl, ##STR2## where Y is O or S; R.sub.2 is alkyl, cycloalkyl, bicycloalkyl, cycloalkenyl, aryl, arylloweralkyl, heteroaryl or heteroarylloweralkyl, R.sub.3 is H or alkyl, or the group --NR.sub.2 R.sub.3 taken as a whole is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-piperazinyl, 4-methyl-1-piperazinyl or 2-(2,6-dichlorophenylimino)-1-imidazolidinyl) and R.sub.4 is hydrogen, loweralkyl, arylloweralkyl, diarylloweralkyl, aryl or heteroaryl,

(c) m is 1 or 2;

(d) each Z is independently H, loweralkyl, halogen, nitro, --NH.sub.2, loweralkylcarbonylamino, arylcarbonylamino, loweralkoxycarbonylamino or loweralkylamino, and

(e) R.sub.1 is H, loweralkyl, arylloweralkyl, heteroarylloweralkyl, cycloalkylmethyl or loweralkenylmethyl, with the proviso that when X is O, m is 1, Z is H and R.sub.1 is methyl, R is not --CONHCH.sub.3, --CONHC.sub.6 H.sub.5, hydrogen, methyl or ethyl, and that when X is O, m is 1 and Z and R.sub.1 are both hydrogen, R is not hydrogen or methyl, and pharmaceutically acceptable acid addition salts thereof which are useful as memory-enhancing and analgesic agents.

L3 ANSWER 9 OF 124 USPATFULL on STN

ACCESSION NUMBER:	94:44647 USPATFULL		
TITLE:	Derivatives of physostigmine, their use and pharmaceutical formulations containing them		
INVENTOR(S):	Bombardelli, Ezio, Milan, Italy		
PATENT ASSIGNEE(S):	Indena S.p.A., Italy (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5314906		19940524
APPLICATION INFO.:	US 1993-2794		19930111 (8)
	NUMBER		DATE
PRIORITY INFORMATION:	GB 1992-5670		19920316
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Brust, Joseph Paul		
ASSISTANT EXAMINER:	Gabilan, MarySusan H.		
LEGAL REPRESENTATIVE:	Kirschstein, Ottinger, Israel & Schiffmiller		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
LINE COUNT:	258		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The therapeutic use of new salts of physostigmine in the treatment of syndromes related to changes in cerebral metabolism in the elderly is described. The new salts of physostigmine, which are based on phosphatidic acid, are highly lipophilic and exhibit excellent bioavailability when administered orally, transcutaneously or transepidermally.

L3 ANSWER 8 OF 124 USPATFULL on STN

ACCESSION NUMBER: 96:68035 USPATFULL

TITLE: Memory enhancing and analgsic 1,2,3,3A,8,8A-Hexahydro--3A, 8(And1,3A,8)-Di (and Tri) Methylpyrrolo(2,3-B Indoles

INVENTOR(S): Hamer, Richard L., Far Hills, NJ, United States
Helsley, Grover C., Pluckemin, NJ, United States
Glamkowski, Edward J., Warren, NJ, United States
Chiang, Yulin, Convent Station, NJ, United States

PATENT ASSIGNEE(S): Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5541216		19960730
APPLICATION INFO.:	US 1992-967534		19921028 (7)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-828751, filed on 31 Jan 1992, now abandoned which is a continuation of Ser. No. US 1988-252309, filed on 3 Oct 1988, now abandoned which is a division of Ser. No. US 1987-49894, filed on 15 May 1987, now patented, Pat. No. US 4791107 which is a continuation-in-part of Ser. No. US 1986-885991, filed on 16 Jul 1986, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Ramsur, Robert W.

LEGAL REPRESENTATIVE: Finnegan, Henderson, Farabow, Garrett & Dunner L.L.P.

NUMBER OF CLAIMS: 25

EXEMPLARY CLAIM: 1

LINE COUNT: 1912

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are described compounds of the formula ##STR1## where (a) X is O or S;

(b) R is H, loweralkyl, ##STR2## where Y is O or S; R.sub.2 is alkyl, cycloalkyl, bicycloalkyl, cycloalkenyl, aryl, arylloweralkyl, heteroaryl or heteroarylloweralkyl, R.sub.3 is H or alkyl, or the group --NR.sub.2 R.sub.3 taken as a whole is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-piperazinyl, 4-methyl-1-piperazinyl or 2-(2,6-dichlorophenylimino)-1-imidazolidinyl) and R.sub.4 is hydrogen, loweralkyl, arylloweralkyl, diarylloweralkyl, aryl or heteroaryl,

(c) m is 1 or 2;

each Z is independently H, loweralkyl, halogen, nitro, --NH.sub.2, loweralkylcarbonylamino, arylcarbonylamino, loweralkoxycarbonylamino or loweralkylamino, and

(e) R.sub.1 is H, loweralkyl, arylloweralkyl, heteroarylloweralkyl, cycloalkylmethyl or loweralkenylmethyl,

with the proviso that when X is O, m is 1, Z is H and R.sub.1 is methyl, R is not --CONHCH.sub.3, --CONHC.sub.6 H.sub.5, hydrogen, methyl or ethyl, and that when X is O, m is 1 and Z and R.sub.1 are both hydrogen, R is not hydrogen or methyl, and pharmaceutically acceptable acid addition salts thereof which are useful as memory-enhancing and analgesic agents.

3 ANSWER 2 OF 124 USPATFULL on STN

ACCESSION NUMBER: 97:52138 USPATFULL

TITLE: Memory enhancing and analgesic 1,2,3,3a,8,8a,-hexahydro-3a,8(and 1,3a,8)-di(and tri)methylpyrrolo[2,3-b] indoles

INVENTOR(S): Hamer, R. Richard L., Far Hills, NJ, United States
Helsley, Grover C., Pluckemin, NJ, United States
Glamkowski, Edward J., Warren, NJ, United States
Chiang, Yulin, Convent Station, NJ, United States

PATENT ASSIGNEE(S): Hoechst-Marion-Roussel, Inc., Kansas City, MO, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5639892		19970617
APPLICATION INFO.:	US 1995-466013		19950606 (8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1992-962079, filed on 16 Oct 1992, now patented, Pat. No. US 5547977 which is a continuation of Ser. No. US 1992-828752, filed on 31 Jan 1992, now abandoned which is a continuation of Ser. No. US 1988-252309, filed on 3 Oct 1988, now abandoned which is a division of Ser. No. US 1987-49894, filed on 15 May 1987, now patented, Pat. No. US 4791107 which is a continuation-in-part of Ser. No. US 1986-885991, filed on 16 Jul 1986, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ramsuer, Robert W.
LEGAL REPRESENTATIVE: Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2102
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There are described compounds of the formula ##STR1## where X is O or S;

(b) R is H, loweralkyl, ##STR2## where Y is O or S; R.sub.2 is alkyl, cycloalkyl, bicyclcalkyl, cycloalkenyl, aryl, arylloweralkyl, heteroaryl or heteroarylloweralkyl, R.sub.3 is H or alkyl, or the group --NR.sub.2.sub.R.sub.3 taken as a whole is 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 4-thiomorpholinyl, 1-piperazinyl, 4-methyl-1-piperazinyl or 2-(2,6-dichlorophenylimino)-1-imidazolidinyl) and R.sub.4 is hydrogen, loweralkyl, arylloweralkyl, diarylloweralkyl, aryl or heteroaryl,

(c) m is 1 or 2;

(d) each Z is independently H, loweralkyl, halogen, nitro, --NH.sub.2, loweralkylcarbonylamino, arylcarbonylamino, loweralkoxycarbonylamino or loweralkylamino, and

(e) R.sub.1 is H, loweralkyl, arylloweralkyl, heheroarylloweralkyl, cycloalkylmethyl or loweralkenylmethyl, with the proviso that when X is O, m is 1, Z is H and R.sub.1 is methyl, R is not --CONHCH.sub.3, --CONHC.sub.6 H.sub.5, hydrogen, methyl or ethyl, and that when X is O, m is 1 and Z and R.sub.1 are both hydrogen, R is not hydrogen or methyl, and, pharmaceutically acceptable acid addition salts thereof which are useful as memory-enhancing and analgesic agents.

L3 ANSWER 57 OF 124 USPATFULL on STN

ACCESSION NUMBER:	1999:121405 USPATFULL			
TITLE:	Use of cholinesterase inhibitors in the treatment of xerostomia			
INVENTOR(S):	Ekstrom, Jorgen, Billdal, Sweden Helander, Herbert, Goteborg, Sweden			
PATENT ASSIGNEE(S):	Astra Aktiebolag, Sodertalje, Sweden (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5962503		19991005	
	WO 9719685		19970605	
APPLICATION INFO.:	US 1996-750825		19961213	(8)
	WO 1996-SE1531		19961125	
			19961213	PCT 371 date
			19961213	PCT 102(e) date
	NUMBER		DATE	
PRIORITY INFORMATION:	SE 1995-4267		19951129	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Henley, III, Raymond			
LEGAL REPRESENTATIVE:	White & Case L.L.P.			
NUMBER OF CLAIMS:	2			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)			
LINE COUNT:	226			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB There is provided the use of a cholinesterase inhibitor in the manufacture of a medicament for topical administration for use in the treatment of xerostomia

L3 ANSWER 56 OF 124 USPATFULL on STN

ACCESSION NUMBER:	1999:124907 USPATFULL
TITLE:	Cholinesterase inhibitors for treatment of Parkinson's disease
INVENTOR(S):	Hutchinson, Michael, New York, NY, United States
PATENT ASSIGNEE(S):	New York University, New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5965571		19991012	
APPLICATION INFO.:	US 1997-915736		19970821	(8)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1996-22746P	19960822	(60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Page, Thurman K.
ASSISTANT EXAMINER:	Channavajjala, Lakshmi
LEGAL REPRESENTATIVE:	Browdy and Neimark
NUMBER OF CLAIMS:	16
EXEMPLARY CLAIM:	1
LINE COUNT:	709

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Parkinson's disease can be treated with an at least one cholinesterase inhibitor. The cholinesterase inhibitor has been found to alleviate both any symptoms of dementia as well as to reduce rigidity and improve motor function.

L3 ANSWER 53 OF 124 USPATFULL on STN

ACCESSION NUMBER:	2000:28013 USPATFULL			
TITLE:	Methods of treating and diagnosing sleep disordered breathing and means for carrying out the method			
INVENTOR(S):	Hedner, Jan, Orangerigatan 4, S-412 66 Goteborg, Sweden Kraiczi, Holger, Viktoriagatan 34, S-411 25 Goteborg, Sweden			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6034117		20000307	
	WO 9722339		19970626	
APPLICATION INFO.:	US 1998-91382		19980921	(9)
	WO 1996-SE1677		19961217	
			19980921	PCT 371 date
			19980921	PCT 102(e) date
	NUMBER		DATE	
PRIORITY INFORMATION:	SE 1995-4537		19951219	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	Granted			
PRIMARY EXAMINER:	Jarvis, William R. A.			
LEGAL REPRESENTATIVE:	Hopgood, Calimafde, Kalil & Judlowe, LLP			
NUMBER OF CLAIMS:	20			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	1 Drawing Figure(s); 1 Drawing Page(s)			
LINE COUNT:	561			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a method for treating snoring, sleep apnea and other form of sleep-disordered breathing, which comprises administration of a therapeutically effective dose of an acetyl choline esterase inhibitor (CEI) such as pyridostigmine or a pharmaceutically acceptable salt thereof.

L3 ANSWER 45 OF 124 USPATFULL on STN

ACCESSION NUMBER:	2001:116582 USPATFULL		
TITLE:	Buccal and sublingual administration of physostigmine		
INVENTOR(S):	Madhat, Maher N., 3305 Grasmere Dr., Lexington, KY, United States 40503		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6264974	B1	20010724
APPLICATION INFO.:	US 1998-111550		19980707 (9)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Kishore, Gollamudi S.		
ASSISTANT EXAMINER:	Channavajjah, Lakshmi		
NUMBER OF CLAIMS:	4		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 1 Drawing Page(s)		
LINE COUNT:	451		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Physostigmine, 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethylpyrrolo[2,3-b] indol-5ol methylcarbamate, administered buccally or sublingually in non-sustained release dosage form provides extremely prolonged blood levels. This active agent is physically compounded with materials of some or all of classes of ingredients that function as pH controls, preservative agents, viscosity control agents, absorption enhancers, stabilizing agents, solvents, and carrier vehicles. This compounding will produce a pharmaceutical composition in the form of a liquid, tablet, gel, patch or lozenge for administration of the active agent, Physostigmine, by absorption through the buccal or sublingual mucosa of the patient. This method of delivery of Physostigmine and similar compounds is useful for treatment of cognitive deficiencies and/or neurological function deficits, mood and/or mental disturbances in mammals including human beings.

L7 ANSWER 1 OF 16 MEDLINE on STN
ACCESSION NUMBER: 96187050 MEDLINE
DOCUMENT NUMBER: 96187050 PubMed ID: 8624119
TITLE: The effect of cholinesterase inhibitors on the secretion of APPS from rat brain cortex.
AUTHOR: Giacobini E; Mori F; Lai C C
CORPORATE SOURCE: Department of Pharmacology, Southern Illinois University School of Medicine, Springfield, Illinois 62794-9230, USA.
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1996 Jan 17) 777 393-8.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960627
Last Updated on STN: 19960627
Entered Medline: 19960614

AB In this study we examined the question whether cholinesterase inhibitors (ChEI) could alter the release of amyloid precursor protein (APP) from superfused brain cortical slices of the rat following electrical as well as pharmacological stimulation with bethanechol (BETHA). Three ChEI, both reversible and irreversible were tested for their ability to enhance the release of non-amyloidogenic soluble derivatives (APPs). These included **physostigmine** (PHY), heptyl-**physostigmine** (HEP) and 2,2-dichlorovinyldimethyl phosphate (DDVP), at the concentrations producing cholinesterase (ChE) inhibition ranging from 5% to 95%. All three ChEI elevated APPs release significantly above control levels. Electrical field stimulation significantly increased the release of APPs within 50 min. Similar increase was observed after muscarinic receptor stimulation with BETHA. Tetrodotoxin (TTX) completely blocked the effect of electrical stimulation. These findings suggest that long-term administration of ChEI to Alzheimer's disease (AD) patients may have a neuroprotective effect by activating normal APP processing and decreasing the formation of amyloidogenic APP products.

L7 ANSWER 2 OF 16 MEDLINE on STN
ACCESSION NUMBER: 95329625 MEDLINE
DOCUMENT NUMBER: 95329625 PubMed ID: 7605915
TITLE: Cholinesterase inhibitors increase secretion of APPs in rat brain cortex.
AUTHOR: Mori F; Lai C C; Fusi F; Giacobini E
CORPORATE SOURCE: Department of Pharmacology, Southern Illinois University School of Medicine, Springfield 62794-9230, USA.
SOURCE: NEUROREPORT, (1995 Mar 7) 6 (4) 633-6.
Journal code: 9100935. ISSN: 0959-4965.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950828
Last Updated on STN: 19950828
Entered Medline: 19950817

AB We examined whether cholinesterase inhibitors (ChEI) could alter the release of amyloid precursor protein (APP) from superfused brain cortical slices of the rat. Three ChEI, both reversible and irreversible, were tested for their ability to enhance the release of nonamyloidogenic soluble derivatives (APPs). These included: **physostigmine** (PHY), heptyl-**physostigmine** (HEP) and 2,2-dichloro-vinyldimethyl phosphate (DDVP), at concentrations producing cholinesterase (ChE) inhibition ranging from 5% to 95%. All three ChEI elevated APPs release significantly above control levels. Electrical field stimulation significantly increased the release of APPs within 50 min. Similar increase was observed after muscarinic receptor stimulation with bethanechol (BETHA). Tetrodotoxin (TTX) completely blocked the effect of electrical stimulation. These findings suggest that administration of ChEI to Alzheimer's disease (AD) patients may have a neuroprotective effect by activating normal APP processing.

L7 ANSWER 3 OF 16 MEDLINE on STN

ACCESSION NUMBER: 96432729 MEDLINE

DOCUMENT NUMBER: 96432729 PubMed ID: 8835781

TITLE: Differential effect of tacrine and **physostigmine** on the secretion of the beta-amyloid precursor protein in cell lines.

AUTHOR: Lahiri D K; Farlow M R

CORPORATE SOURCE: Department of Psychiatry, Indiana University School of Medicine, Indianapolis 46202, USA.

CONTRACT NUMBER: R01AG10297 (NIA)

SOURCE: JOURNAL OF MOLECULAR NEUROSCIENCE, (1996 Spring) 7 (1) 41-9.
Journal code: 9002991. ISSN: 0895-8696.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199612

ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961206

AB The senile plaque in Alzheimer's disease (AD) consists mainly of the amyloid beta-peptide (A beta) derived from a family of large integral membrane glycoproteins, beta-amyloid precursor proteins (beta APP). Soluble derivatives of beta APP generated by the proteolytic processing of full-length beta APP are normally secreted into the conditioned medium of cultured cells. Here we have investigated the possibility that the processing of beta APP can be regulated by the cholinesterase inhibitors **physostigmine** and tacrine. Both drugs mildly improve cognitive functions in some patients with AD. We analyzed the level of beta APP in glial, neuroblastoma, and pheochromocytoma cells by immunoblotting cell lysates and conditioned media using a monoclonal antibody, MAb22C11. The levels of soluble beta APP derivatives normally present in conditioned media were severely inhibited by treating cells with tacrine but not with **physostigmine**. Whereas the treatment of cells with tacrine resulted in a small decrease in the intracellular levels of beta APP, treating cells with **physostigmine** resulted in a slight increase in the intracellular levels of beta APP compared to untreated cells. The effect of tacrine on the secretion of beta APP was not affected by cotreating cells with muscarinic agents, staurosporine, or the calcium ionophore. Our results suggest that a decrease in the secretion of beta APP by tacrine did not depend on its anticholinesterase activity and that tacrine operates via a noncholinergic mechanism.

L7 ANSWER 4 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001481220 MEDLINE
DOCUMENT NUMBER: 21415852 PubMed ID: 11524148
TITLE: Reduction of cortical amyloid beta levels in guinea pig brain after systemic administration of **physostigmine**.
AUTHOR: Beach T G; Kuo Y M; Schwab C; Walker D G; Roher A E
CORPORATE SOURCE: Sun Health Research Institute, 10515 West Santa Fe Drive, Sun City, AZ 85372, USA.. tbeach@mail.sunhealth.org
SOURCE: NEUROSCIENCE LETTERS, (2001 Sep 7) 310 (1) 21-4.
Journal code: 7600130. ISSN: 0304-3940.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010830
Last Updated on STN: 20011029
Entered Medline: 20011025

AB Overproduction of the peptide amyloid beta (Abeta) is thought to be a critical pathogenetic event in Alzheimer's disease (AD). Decreasing A production may therefore slow or halt the progression of AD. In vitro work has indicated that cholinergic muscarinic receptor agonists may reduce cellular production of Abeta. Here we show that systemic administration of **physostigmine**, an acetylcholinesterase inhibitor, lowers Abeta levels in vivo. Guinea pigs treated for 10 days with s.c. **physostigmine** had levels of cortical AbetaN-40 and N-42 which were 57% and 72%, respectively, of those in control animals. Levels of cortical beta-amyloid precursor protein were not significantly affected by drug treatment. These results suggest that cholinergic therapy may affect the course of AD by limiting Abeta accumulation.

L7 ANSWER 5 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001301896 MEDLINE
DOCUMENT NUMBER: 21125031 PubMed ID: 11226396
TITLE: Dehydroevodiamine attenuates beta-amyloid peptide-induced amnesia in mice.
AUTHOR: Wang H H; Chou C J; Liao J F; Chen C F
CORPORATE SOURCE: Department and Institute of Pharmacology, National Yang-Ming University, No. 155, Sec. 2, Li-Nong Street, Pei-Tou Dist. (112), Taipei (11221), Taiwan.
SOURCE: EUROPEAN JOURNAL OF PHARMACOLOGY, (2001 Feb 16) 413 (2-3) 221-5.
Journal code: 1254354. ISSN: 0014-2999.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB Dehydroevodiamine has been reported to have anticholinesterase activity and an anti-amnesic effect. This study examined the effects of dehydroevodiamine on scopolamine- and beta-amyloid peptide-(25--35)-induced amnesia in mice, using a step-through passive avoidance test. Similarly to the cholinesterase inhibitor, **physostigmine** (0.03--0.3 mg/kg, i.p.), dehydroevodiamine (0.75--12.0 mg/kg, i.p.) administered 30 min before the training trial, immediately after the training trial, and 30 min before the retention test significantly improved scopolamine- and beta-amyloid peptide-(25--35)-induced amnesia. In beta-amyloid peptide-(25--35)-induced amnesia, the rank order of anti-amnesic potency in these three administration schedules for dehydroevodiamine was different from that for **physostigmine**.

Furthermore, dehydroevodiamine was more potent to improve beta-amyloid peptide-(25--35)-induced amnesia than scopolamine-induced amnesia when administered before the training trial. These results suggested that dehydroevodiamine may have an action other than that of an anticholinesterase and may be a novel and effective ligand for improvement of beta-amyloid type amnesia.

L7 ANSWER 6 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2003053998 MEDLINE
DOCUMENT NUMBER: 22414648 PubMed ID: 12527333
TITLE: beta-Amyloid aggregation induced by human acetylcholinesterase: inhibition studies.
AUTHOR: Bartolini Manuela; Bertucci Carlo; Cavrini Vanni; Andrisano Vincenza
CORPORATE SOURCE: Dipartimento di Scienze Farmaceutiche, Universita di Bologna, Via Belmeloro 6, 40126 Bologna, Italy.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (2003 Feb 1) 65 (3) 407-16.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030205
Last Updated on STN: 20030214
Entered Medline: 20030213

AB The aggregation of beta-amyloid (1-40) (Abeta) induced by human recombinant acetylcholinesterase (HuAChE) was studied by means of circular dichroism (CD) and by thioflavin T fluorescence spectroscopy. Abeta was incubated alone and with HuAChE. The kinetic of fibrils formation was followed for 48 hr. The increasing beta-conformation content induced by HuAChE, preliminary to the formation of Abeta fibrils, was determined by circular dichroism. This phenomenon was found to be related to the thioflavin T emission of fluorescence at 490 nm. Incubation experiments were performed in the presence of known AChE inhibitors (**physostigmine**, edrophonium, decamethonium, propidium) and drugs used for Alzheimer's disease (AD) (tacrine, donepezil), to test their capability of preventing the HuAChE-induced Abeta aggregation. The non-competitive or mixed mode of AChE inhibition was confirmed to be an essential feature. At 100 microM propidium, decamethonium, donepezil and **physostigmine** were found to inhibit the HuAChE-induced Abeta aggregation by 82, 25, 22 and 30%, respectively.

L7 ANSWER 7 OF 16 MEDLINE on STN
ACCESSION NUMBER: 97470298 MEDLINE
DOCUMENT NUMBER: 97470298 PubMed ID: 9329715
TITLE: Effects of cholinesterase inhibitors on the secretion of beta-amyloid precursor protein in cell cultures.
AUTHOR: Lahiri D K; Farlow M R; Nurnberger J I Jr; Greig N H
CORPORATE SOURCE: Department of Psychiatry, Indiana University School of Medicine, Indianapolis 46202, USA..
DLAHIRI@INDYVAX.IUPUI.EDU
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1997 Sep 26) 826 416-21.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971113

AB One of the main characteristics of Alzheimer's disease (AD) is the

cerebrovascular deposition of the amyloid beta-peptide (A beta), which is derived from a larger beta-amyloid precursor protein (beta APP). The majority of beta APP is processed by either a secretory of lysosomal/endosomal pathway. Carboxyl-truncated soluble derivatives of beta APP (sAPP) are generated by the proteolytic processing of full-length beta APP by either alpha- or beta-secretase enzyme. Our objective is to determine whether the processing of beta APP can be regulated by cholinesterase inhibitors, some of which were shown to produce a moderate improvement in memory and cognitive functions in patients with Alzheimer's disease. Here we have analyzed the levels of sAPP derivatives in cultured cells treated with different drugs by immunoblotting samples of conditioned media. The immunoreactive protein bands were developed by probing with the monoclonal antibody 22C11. Treating neuroblastoma, pheochromocytoma and fibroblast cells with high dose of either 3,4-diaminopyridine, metrifonate, or **physostigmine** did not inhibit the secretion of sAPP. Treating glioblastoma with either 3,4-diaminopyridine or metrifonate showed an increase in secretion of sAPP. However, treatment of cells with tacrine reduced release of sAPP in conditioned media of cell lines studied. The difference in action of metrifonate, **physostigmine**, and tacrine on beta APP is independent of their anticholinesterase activities. Our results suggests that noncatalytic functions of cholinesterase inhibitors can be utilized to alter the metabolism of beta APP, which might in turn affect the process of deposition of A beta, a key component of the cerebrovascular amyloid detected in AD.

L7 ANSWER 8 OF 16 MEDLINE on STN
ACCESSION NUMBER: 93391425 MEDLINE
DOCUMENT NUMBER: 93391425 PubMed ID: 8378353
TITLE: Amyloid precursor protein in the cerebral cortex is rapidly and persistently induced by loss of subcortical innervation.
AUTHOR: Wallace W; Ahlers S T; Gotlib J; Bragin V; Sugar J; Gluck R; Shea P A; Davis K L; Haroutunian V
CORPORATE SOURCE: National Institute of Mental Health Neuroscience Center at St. Elizabeths Hospital, Washington, DC 20032.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 Sep 15) 90 (18) 8712-6. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931105
Last Updated on STN: 19980206
Entered Medline: 19931020

AB Lesions of the cholinergic nucleus basalis of Meynert elevate the ex vivo synthesis of beta amyloid precursor protein (beta-APP) in the cerebral cortex, a major projection region. We have found that this elevation is reflected by increased levels of beta-APP mRNA. The induction is rapid (occurring 60 min after placement of the lesion) and persistent (remaining for at least 45 days after lesioning). Two other subcortical lesions, which result in reductions of cortical adrenergic and serotonergic innervation, similarly induced cortical beta-APP. The beta-APP induction is reversible and does not require loss of the subcortical neurons. Infusion of lidocaine, a calcium antagonist that disrupts neurotransmitter release, into the nucleus basalis of Meynert leads to the temporary reduction of released acetylcholine in the cortex. In this model, beta-APP mRNA levels are elevated shortly after the infusion of lidocaine (90 min) but return to preinfusion levels 7 days after the lidocaine treatment. However, metabolic stresses of the brain, including chronic **physostigmine**, glucocorticoid, and diabetogenic treatments, fail to induce the beta-APP response. These results suggest that the induction

of beta-APP is a specific response to the loss of functional innervation in the cortex. Importantly, these studies show that cortical beta-APP is induced by lesions that mimic the neurochemical deficits most frequently observed in Alzheimer disease.

L7 ANSWER 9 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001362088 MEDLINE
DOCUMENT NUMBER: 21315831 PubMed ID: 11422374
TITLE: Oxidative and hydrolytic properties of beta-amyloid.
AUTHOR: Brzyska M; Bacia A; Elbaum D
CORPORATE SOURCE: Laboratory of Bio-Physical Methods, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland.. mbrzyska@nencki.gov.pl
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (2001 Jun) 268 (12) 3443-54.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB beta-Amyloid protein is the major component of senile plaques found in the brains of Alzheimer's patients. Previously, a new biochemical property of amyloid, its ability to disrupt ester and peptide bonds, was described [Elbaum, D., Brzyska, M., Bacia, A. & Alkon, D. (2000) Biochem. Biophys. Res. Commun. 267, 733-738]. In the present work we compare the ability of beta-amyloid to hydrolyse and oxidize model fluorescent derivatives of dichlorofluorescein [dichlorodihydrofluorescein (H2DCF) or dichlorofluorescein diacetate (DCF-DA), respectively] to the same final product (dichlorofluorescein). Although there is accumulating evidence of oxidative properties of beta-amyloid, little is known about its hydrolytic abilities. Chemical modification studies revealed that hydrolytic properties are related to a His, Ser and Asp/Glu triad, while residues of His, Tyr and Met are involved in the oxidative activity of amyloid. Studies with the rat homologue of human beta-amyloid (1-40), containing three amino-acid substitutions (Arg5-->Gly, Tyr10-->Phe and His13-->Arg) confirmed a role of His in the studied processes. Reduction of the hydrolysis product caused by inhibitors of Ser esterases (phenylmethylsulphonyl fluoride and **eserine**) suggests that beta-amyloid-mediated hydrolysis is Ser sensitive. Antioxidants and metal chelators that reduced H2DCF oxidation did not change or increase DCF-DA hydrolysis. Solvent isotope effects suggest the involvement of hydrogen bonds in the hydrolysis reaction. Hydrolysis was inhibited by redox-active metal ions and was practically oxygen independent while the oxidation process was redox-active-metal enhanced [Cu(II) and Fe(II) primarily], and oxygen dependent. Product formation was significantly inhibited by catalase and superoxide dismutase as well as benzoquinone, a specific superoxide anion radical scavenger. Increase of fluorescence by oxidation was strongly inhibited by azide and His and enhanced in samples prepared with deuterated phosphate buffer, suggesting singlet oxygen intermediacy. Our data are consistent with superoxide-mediated singlet oxygen intermediate in this Fenton mechanism-driven reaction. These results indicate that hydrolytic and oxidative properties of beta-amyloid are distinct features of this peptide and probably require different mechanisms to occur, but both of them may contribute to beta-amyloid toxicity.

L7 ANSWER 10 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001173694 MEDLINE
DOCUMENT NUMBER: 21158258 PubMed ID: 11273593
TITLE: Cholinesterase inhibitors, beta-amyloid precursor protein

and amyloid beta-peptides in Alzheimer's disease.
AUTHOR: Lahiri D K; Farlow M R; Hintz N; Utsuki T; Greig N H
CORPORATE SOURCE: Department of Psychiatry, Indiana University School of Medicine, Indianapolis 46202, USA.
SOURCE: ACTA NEUROLOGICA SCANDINAVICA. SUPPLEMENTUM, (2000) 176 60-7.
Journal code: 0370337. ISSN: 0065-1427.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB The extracellular deposition of amyloid beta-peptide (Abeta) in the form of cerebrovascular amyloid and extracellular plaques is one of the major neuropathological manifestations of Alzheimer's disease (AD). Abeta is generated proteolytically from the large beta-amyloid precursor protein (APP). APP is cleaved by a group of proteases called "secretase" to generate soluble derivatives of APP (sAPP), which are secreted in human plasma, CSF and cultured cells. Neurochemically, there is a severe loss of cholinergic neurons and a decreased synthesis of acetylcholine in neocortex in AD. Current approved AD drugs, such as aricept and tacrine, are based on the use of cholinesterase inhibitors (ChEIs) and have been reported to improve memory deficits and cognitive decline in some patients with AD. To compare the effects of ChEIs on APP processing, we have tested a series of ChEIs such as tacrine, **physostigmine**, metrifonate, phenserine and cymserine in cultured human neuroblastoma cells. We analyzed levels of sAPP by immunochemical techniques with APP-specific antibodies and assayed levels of Abeta by a sensitive sandwich ELISA. Based on these results, ChEIs can be divided into three groups: the first group of ChEIs had no effect on sAPP secretion, the second decreased the sAPP secretion only, and third group affected the secretion of sAPP and Abeta. The difference in the action of metrifonate, **physostigmine**, phenserine and tacrine on APP processing is independent of their selectivity for the cholinesterase enzymes. This possibly is due to the different targets that are used by ChEIs. Studying the effects of ChEIs on different targets is useful to maximize the benefit of ChEIs for the treatment of AD subjects.

L7 ANSWER 11 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2000139719 MEDLINE
DOCUMENT NUMBER: 20139719 PubMed ID: 10673360
TITLE: Implication of novel biochemical property of beta-amyloid.
AUTHOR: Elbaum D; Brzyska M; Bacia A; Alkon D L
CORPORATE SOURCE: Laboratory of Biophysical Methods, Nencki Institute of Experimental Biology, Warsaw, Poland.. elbaum@nencki.gov.pl
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Jan 27) 267 (3) 733-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000309

AB Alzheimer disease (AD) is a heterogeneous disorder with a variety of molecular pathologies converging predominantly on abnormal amyloid deposition particularly in the brain. beta-Amyloid aggregation into senile plaques is one of the pathological hallmarks of AD. beta-Amyloid is generated by a proteolytic cleavage of a large membrane protein, amyloid

precursor protein (APP). We have observed a new property of beta-amyloid. The amyloid 1-42 beta fragment, when aggregated, possesses proteolytic and esterase-like activity, in vitro. Three independent methods were used to test the new property of beta-amyloid. While esterase activity involves imidazole catalysis, proteolytic activity is consistent with participation of a serine peptidase triad: catalytic Ser, His and Glu (or Asp). Although the amino acid triad is a necessary requirement for the protease reactivity, it is not sufficient since the secondary structure of the protein significantly contributes to the proteolytic activity. The ability of beta-amyloid to cleave peptide or ester bonds could be thus responsible for either inactivation of other proteins and/or APP proteolysis itself. This property may be responsible for early pathogenesis of AD since there is emerging evidence that non-plaque amyloid is elevated in Alzheimer patients.

L7 ANSWER 12 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001077065 MEDLINE
DOCUMENT NUMBER: 21003610 PubMed ID: 11117548
TITLE: The selective muscarinic M1 agonist AF102B decreases levels of total Abeta in cerebrospinal fluid of patients with Alzheimer's disease.
AUTHOR: Nitsch R M; Deng M; Tennis M; Schoenfeld D; Growdon J H
CORPORATE SOURCE: Division of Psychiatry Research, University of Zurich, Switzerland.
CONTRACT NUMBER: 5-MO1-01066-23 (NIA)
P50 AG 05134
SOURCE: ANNALS OF NEUROLOGY, (2000 Dec) 48 (6) 913-8.
Journal code: 7707449. ISSN: 0364-5134.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

AB beta-Amyloid (Abeta) deposits in diffuse and compact senile plaques in the brain are one of the defining histopathological features of Alzheimer's disease (AD). Preventing Abeta deposition is a goal of drug therapy for AD, because excessive amounts of Abeta may be toxic to neurons. In preclinical studies, activation of the muscarinic M1 receptor subtype inhibited Abeta secretion from cultured cells. To determine whether a similar sequence occurs in human beings, we administered the selective M1 agonist AF102B to 19 AD patients and measured total Abeta (Abeta(total)) levels in cerebrospinal fluid (CSF) before and during treatment. Abeta(total) levels in CSF decreased in 14 patients by 22%, increased in 3 patients, and were unchanged in 2 patients; the overall decrease in the group as a whole was statistically significant. To test the specificity of the M1 effect, we also measured the relative changes in Abeta(total) levels in CSF during treatments in separate sets of AD patients with the acetylcholinesterase inhibitor **physostigmine** or the anti-inflammatory drug hydroxychloroquine. CSF Abeta(total) levels did not change significantly in the 9 AD patients in the **physostigmine** protocol or in the 10 AD patients in the hydroxychloroquine study. These data provide evidence that the activation of M1 receptors reduces Abeta levels in the CSF of AD patients. If this effect also occurs in brain, M1 agonists may have long-term therapeutic benefits by lowering amyloid in AD.

L7 ANSWER 13 OF 16 MEDLINE on STN
ACCESSION NUMBER: 97334393 MEDLINE
DOCUMENT NUMBER: 97334393 PubMed ID: 9191090
TITLE: Pharmacological modulation of Alzheimer's beta-amyloid

precursor protein levels in the CSF of rats with forebrain cholinergic system lesions.

AUTHOR: Haroutunian V; Greig N; Pei X F; Utsuki T; Gluck R; Acevedo L D; Davis K L; Wallace W C

CORPORATE SOURCE: Department of Psychiatry, Mount Sinai School of Medicine and Bronx VA Medical Center, NY 10468, USA.

CONTRACT NUMBER: R01-AG10138 (NIA)

SOURCE: BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1997 Jun) 46 (1-2) 161-8.
Journal code: 8908640. ISSN: 0169-328X.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199708

ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19980206
Entered Medline: 19970805

AB Abnormal deposition and accumulation of Alzheimer's amyloid beta-protein (A beta) and degeneration of forebrain cholinergic neurons are among the principal features of Alzheimer's disease. Studies in rat model systems have shown that forebrain cholinergic deficits are accompanied by induction of cortical beta-amyloid precursor protein (beta-APP) mRNAs and increased levels of secreted beta-APP in the CSF. The studies reported here determined whether the CSF levels of secreted beta-APP could be altered pharmacologically. In different experiments, rats with lesions of the forebrain cholinergic system received injections of vehicle, a muscarinic receptor antagonist scopolamine, or one of two cholinesterase inhibitors - diisopropyl phosphorofluoridate (DFP) or phenserine. Scopolamine was administered to determine whether the levels of beta-APP in the CSF could be increased by anticholinergic agents. The cholinesterase inhibitors were administered to determine whether the forebrain cholinergic system lesion-induced increases in CSF beta-APP could be reduced by cholinergic augmentation. Scopolamine administration led to a significant increase in the CSF levels of secreted beta-APP in sham-lesioned rats. Phenserine, a novel, reversible acetyl-selective cholinesterase inhibitor, significantly decreased the levels of secreted beta-APP in the CSF of forebrain cholinergic system-lesioned rats whereas DFP, a relatively non-specific cholinesterase inhibitor, failed to affect CSF levels of secreted beta-APP. These results suggest that the levels of secreted beta-APP in the CSF can be pharmacologically modulated but that this modulation is dependent upon the status of the forebrain cholinergic system and the pharmacological properties of the drugs used to influence it.

L7 ANSWER 14 OF 16 MEDLINE on STN

ACCESSION NUMBER: 2001366104 MEDLINE

DOCUMENT NUMBER: 21309945 PubMed ID: 11404470

TITLE: Phenserine regulates translation of beta -amyloid precursor protein mRNA by a putative interleukin-1 responsive element, a target for drug development.

AUTHOR: Shaw K T; Utsuki T; Rogers J; Yu Q S; Sambamurti K; Brossi A; Ge Y W; Lahiri D K; Greig N H

CORPORATE SOURCE: Drug Design and Development, Laboratory of Neurosciences, National Institute on Aging, Baltimore, MD 21224, USA.

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2001 Jun 19) 98 (13) 7605-10.
Journal code: 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200107

ENTRY DATE: Entered STN: 20010730

Last Updated on STN: 20030105
Entered Medline: 20010726

AB The reduction in levels of the potentially toxic amyloid-beta peptide (Abeta) has emerged as one of the most important therapeutic goals in Alzheimer's disease. Key targets for this goal are factors that affect the expression and processing of the Abeta precursor protein (betaAPP). Earlier reports from our laboratory have shown that a novel cholinesterase inhibitor, phenserine, reduces betaAPP levels in vivo. Herein, we studied the mechanism of phenserine's actions to define the regulatory elements in betaAPP processing. Phenserine treatment resulted in decreased secretion of soluble betaAPP and Abeta into the conditioned media of human neuroblastoma cells without cellular toxicity. The regulation of betaAPP protein expression by phenserine was posttranscriptional as it suppressed betaAPP protein expression without altering betaAPP mRNA levels. However, phenserine's action was neither mediated through classical receptor signaling pathways, involving extracellular signal-regulated kinase or phosphatidylinositol 3-kinase activation, nor was it associated with the anticholinesterase activity of the drug. Furthermore, phenserine reduced expression of a chloramphenicol acetyltransferase reporter fused to the 5'-mRNA leader sequence of betaAPP without altering expression of a control chloramphenicol acetyltransferase reporter. These studies suggest that phenserine reduces Abeta levels by regulating betaAPP translation via the recently described iron regulatory element in the 5'-untranslated region of betaAPP mRNA, which has been shown previously to be up-regulated in the presence of interleukin-1. This study identifies an approach for the regulation of betaAPP expression that can result in a substantial reduction in the level of Abeta.

L7 ANSWER 15 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2001178474 MEDLINE
DOCUMENT NUMBER: 21074696 PubMed ID: 11204417
TITLE: Chronic intracerebroventricular exposure to beta-amyloid(1-40) impairs object recognition but does not affect spontaneous locomotor activity or sensorimotor gating in the rat.
AUTHOR: Nag S; Tang F; Yee B K
CORPORATE SOURCE: Department of Physiology, Faculty of Medicine, University of Hong Kong, PR China.
SOURCE: EXPERIMENTAL BRAIN RESEARCH, (2001 Jan) 136 (1) 93-100. Journal code: 0043312. ISSN: 0014-4819.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB This study examined the cognitive effects of chronic in vivo exposure to beta-amyloid(1-40) via the intracerebroventricular route on two distinct paradigms. The first test evaluated a form of early attentional control referred to as sensorimotor gating in which an antecedent weak prepulse stimulus modulates the reactivity to a subsequent startle-eliciting stimulus. The second test utilized the spontaneous preference for a novel object over that of a familiar one in rats as a measure of object recognition memory. We found that beta-amyloid exposure leads to a severe deficit in the object memory test but spares sensorimotor gating. Moreover, unlike the water maze deficit induced by beta-amyloid (Nag et al., in preparation), the deficit on object recognition was resistant to amelioration by systemic **physostigmine** treatment at a dose of 0.06 mg/kg per day intraperitoneally. The present results add to previous reports that beta-amyloid exposure can lead to deficits on hippocampal lesion sensitive tasks, suggesting that dysfunction of the rhinal cortices in addition to that of the septohippocampal system is implicated in

beta-amyloid-induced behavioral impairments. It therefore lends support to the hypothesis that beta-amyloid exposure can lead to severe impairment across multiple memory systems.